Ventilatory impairments associated with Parkinson's Disease: a systematic review and meta-analysis

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Short title: Ventilatory impairments in Parkinson Disease

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Abstract

Background: The peripheral and central repercussions of Parkinson Disease (PD) affect the neuromuscular system producing a loss of muscle strength that can influence the respiratory system. Although several studies have examined various respiratory aspects of PD, to the best of our knowledge no study to date has systematically reviewed the existing data.

Objectives: To examine the available literature related to the respiratory impairment in PD patients.

Methods: We used PRISMA guidelines when reporting this review. We searched Pubmed, Cinhal, SciELO, and Cochrane Library, from inception until August 2018. Main variables assessed were Forced Vital Capacity Percent predicted (FVC %), and Forced Expiratory Volume in One Second Percent predicted (FEV_1%) for PD patients.

Results: Six studies were included in this systematic review and meta-analysis. The obtained results concluded that PD patients present poorer pulmonary function when compared to healthy controls. When PD patients were compared between ON and OFF states, the results reviewed are in favour to ON state. In the meta-analysis performed for FVC% and FEV_1%, the results fail to found significant differences between PD patients and controls (p=0.336 and p=0.281, respectively), and between PD ON and OFF states (p=0.109 and p=0.059, respectively).

Conclusions: We conclude that PD patients have impaired respiratory capacities that are related to the PD severity, time since diagnosis and OFF state. Adequate follow up of the respiratory function and studies focused on PD phenotypes have to be considered in future studies.

Prospero registration: ID=CRD42018105121

Introduction

Among neurodegenerative diseases, Parkinson disease (PD) has a high incidence and rate of disability. Although the clinical presentation and evolution of PD patients are heterogeneous, the disability associated with it has different causes involving gradual loss of motor and non-motor function associated with this pathology [1].

PD is characterized by a profound and selective loss of nigrostriatal dopaminergic neurons that provokes motor symptoms consisting in the cardinal triad of bradykinesia, rigidity, and tremor; accompanied by non-motor symptoms such as mood changes, cognitive decline, pain, sleep disturbance, and autonomic dysfunction [2]. The related peripheral and central repercussions of PD affect the neuromuscular system showing loss of movement control and muscle strength that can influence the respiratory system [3].

Some care guidelines regarding breathing for the adults patients with neuromuscular [4,5,6] and/or neurodegenerative diseases [7,8] have been published, but they do not provide sufficient detail about the impairments, rationale, or the best treatments for these types of patients.

Different studies have reported aspiration pneumonia among other complications due to the respiratory dysfunction as the most frequent causes of death in PD patients [9] and, aspiration is clearly related to the dysfunction of the protective systems of the upper airways [10]. In fact, the incidence of pneumonia is usually accompanied with deterioration of pharyngeal, laryngeal and respiratory muscles as well as protective reflexes like the cough reflex. The cough creates an important expiratory airflow that is of great importance in preventing respiratory complications in PD [11]. Additionally, other signs and symptoms like dysphagia, impaired speech and phonation have been related to the respiratory impairment in PD [12,13].

The medical management of PD involves levodopa that improves the motor and non-motor symptoms of PD, but the observed improvements use to fluctuate based on dopaminergic administration and compliance. In fact, studies examining particular signs and symptoms during on and off dopaminergic treatment (ON state and Off state, respectively) have found poorer results during Off state.

Although several studies have examined different characteristics of ventilation related to clinical aspects of PD [14,15], to the best of our knowledge no study to date has systematically reviewed the existing data as it relates directly to respiratory impairments. The purpose of the present study was to systematically review the literature and provide an updated and more comprehensive review related to respiratory impairment in patients with PD taking into account medication effectiveness fluctuation. Additionally, a meta-analysis will be performed in order to analyze the impairments found among the different PD populations.

Materials and Methods

The protocol for this systematic review was been developed consistently with the Preferred Reporting Items for Systematic Review checklist (PRISMA). This review was registered in the International Prospective Register of Systematic Reviews (PROSPERO Registration: ID:CRD42018105121).

Search Strategy

One researcher undertook the initial literature search, scanning all the abstracts to identify eligible studies. If it was unclear to include some of the studies, advice was sought from a second researcher and a consensus opinion made. We performed a systematic review of the available literature in Pubmed, Cinahl, SciELO and Cochrane library with the appropriate search terms. Relevant publications were identified by searching the PubMed, Cinahl and Cochrane library bibliographic databases from inception until August 2018 with combinations of the keywords “pulmonary function AND Parkinson”, “lung AND Parkinson”, “breathing disorders AND Parkinson” (excluding nocturnal disorders), “ventilation AND Parkinson”.

Study Selection Process

Articles were included if they met the following criteria: (1) the sample population consisted in Parkinson disease patients, (2) pulmonary function had to be compared between patients and controls, or compared between ON and OFF states and (3) primary variables had to be Forced Vital Capacity (FVC%) and Forced Expiratory Volume in One Second (FEV_1%) both predicted.

Screening of the titles and abstracts of the retrieved studies for relevance was performed by two reviewers, and discrepancies were resolved by consensus. Articles published in languages other than English, French, Spanish or Portuguese were excluded after the title and abstract screen. Structured abstracts and posters were also excluded. Two reviewers reviewed the remaining articles in their entirety for consistency with the study protocol

Quality Assessment and Data Extraction

Two reviewers independently assessed the quality of the studies using the Newcastle-Ottawa Quality Assessment Scale, a simple and widely used tool that scores the methods of observational studies on a scale of 0 (very poor) to 9 (rigorous)[16].

Statistical analysis

Where appropriate, study results were pooled and a meta-analysis was undertaken using Review Manager software (RevMan version 5.1, updated March 2011). The meta-analysis was limited owing to the clinical heterogeneity of the included studies. The I^2 statistic was utilized to determine the degree of heterogeneity, where the percentages quantified the magnitude of heterogeneity: 25% = low, 50% = medium, and 75% = high heterogeneity. Using this scale, if I^2 was 50%, a random effects model was used. All the included variables were of continuous data (FVC% and FEV_1%) and the MD with 95% CI was used in analysis.

Results

PRISMA flow chart (figure 1) shows the number of papers identified on Pubmed, Cinhal, SciELO, and the Cochrane Library, the steps performed in the study selection process, and the reasons for article exclusion.

Please, insert figure 1

A total of 815 studies were retrieved from the electronic search and other sources. From these, 809 studies were excluded due to design, duplicated titles, or absence of the variables of interest. A total of 6 studies [17,18,19,20,21,22] were included in the analysis.

Risk of bias

The subscores of the Newcastle-Ottawa Quality Assesment Scale and total scores for each study are presented in Table 1. The studies presented a moderate quality with a range from 6 to 9 points.

The majority of the studies evaluated fail to refer comparability of cases and controls on the basis of the design or analysis.

Please insert Table 1

Table 2 summarizes participants' demographic and clinical characteristics (severity and duration), respiratory variables and results.

Please insert Table 2

The majority of the patients included in the studies have a moderate PD severity, with only two studies including mild and severe subjects. The age of the patients included range from 51 to 69 years and male gender.

Additionally to the main variables, cough effectiveness (PEF), respiratory muscle strength (PIM, SNIP), and physiological response to hypercapnia measures were also included in some studies and considered as secondary variables.

Results obtained when comparing PD patients and controls

Of the studies that compare PD patients and healthy subjects [17,20,21], two of them conclude that FVC% and FEV_1% were significantly worse in PD. Curiously the study of Baille et al [17] shows contrary results for the similar variables in favour to PD subjects. Nevertheless, the pooled

analysis showed no significant differences between the groups in FVC% (MD 0.81, 95% CI, -0.84 to 2.45; I^2= 96.59, p=0.336) (figure 2) and in FEV_1% (MD 0.75, 95% CI, -1.62 to 2.12; I^2=95.29, p=0.281) (figure 3).

Please, insert the figure 2 and 3

In the case of the reported secondary variables respiratory muscle strength was evaluated. Baille et al. [17] concluded that PD patients obtained significantly worse results compared to healthy controls in Maximal Inspiratory Pressure and Sniff Nasal Inspiratory Pressure. In the comparisons between PD phenotypes slight differences were found between tremoric and akinetic phenotypes.

Results obtained when comparing PD patients in ON and OFF state

Four studies evaluated FVC% and FEV_1% in PD patients during On and Off treatment states [18,19,21,22]. The majority of them concluded that PD ON groups obtained significantly higher values compared to PD OFF groups, but the study of Hampson et [19] al shows contrary results. In this line, the pooled analysis showed no significant differences between the groups in FVC% (MD 0.25, 95% CI,-0.06 to 0.56; I^2 =41.71%, p=0.109) (figure 4) and in FEV_1% (MD 0.21 , 95% CI,-0.01 to 0.42 ; I^2 = 10.43%, p=0.059) (figure 5). A sensitive analysis showed that this heterogeneity in the FVC% was mainly due to the magnitude of the effect found in the study by Hampson et al. [19]. When this study was excluded, the I^2 of the pooled effect became 32.32% with an SMD of 0.40 (95% CI=0.06, 0.74 ; p=0.003).

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Furthermore, with respect to other spirometric values (TLC, RV), gasometric, and cough measurements the obtained results are in favour to ON state groups.

De Pandis et al. [22] compared pH, PaO2 and PaCO2 in PD patients ON and OFF states, obtaining significantly higher values the PD ON group.

Discussion

This systematic review and meta-analysis aimed to examine the available literature related to the respiratory impairment in patients with PD. The obtained results concluded that PD patients present poorer pulmonary function when compared to healthy controls. When PD patients were compared between ON and OFF states, the results reviewed are in favour to ON state. Those results have been found significant only for some respiratory variables (FVC, FEV1, FEV1/FVC and PEF) and in the more severe PD patients.

In the meta-analysis performed for FEV_1% and FVC%, the results fail to found significant differences between PD patients and controls and between PD states, this can be due to the heterogeneity of the groups PD profile and to the severity of the disease.

Respiratory differences between PD patients and controls

The characteristics of the patients compared to controls were variable across the studies included. In the majority of the cases, the severity of the disease was moderate to severe found significant differences between PD patients and controls for all measured variables. The study of Baille includes mild severity and promptly diagnosed PD patients, failing to found the same conclusions for respiratory variables. In Baille study the comparisons between PD and control groups found significant impairments in respiratory muscle strength in favour to controls and significant better results for respiratory function in favour to PD patients.

The cough effectiveness was compared with controls in the study of Sathyaprabha, found significant differences between groups in favour to controls. This fact has been previously reported when prevalence of pneumonia in PD patients has been discussed [9].

The results obtained in the meta-analysis when compared PD to controls in FEV_1% and FVC% measures, shows no significant differences between groups. This fact could be explained to the heterogeneity of the stage and diagnosis of the PD subjects included. In this line the study of

Baille has been determinant to the results obtained. In view of these results, PD patients with similar severity, pulmonary impairments can be additionally determined by the disease duration. In fact, a study carried out by Wang et al [23] found a significant relationship between respiratory impairments and PD duration.

Respiratory differences between PD patients in ON/OFF state

When comparing ON and OFF states among Parkinson patients we found that patients with PD On state present better pulmonary function compared to patients with PD Off state. Both restrictive and obstructive patterns of pulmonary dysfunction have been described in patients with PD [9]. However, even though levodopa has been considered as the gold standard treatment for PD since its discovery in the early 1960s, their effects on pulmonary function in PD patients remain controversial [24].

This was significant in the studies of De Pandis, Sathyaprabha and Tambasco for FEV_1%, FVC%, cough efficacity and gasometric variables. The included PD patients in those studies were similar in PD severity, age of participants and time since diagnosis. In contrast, the study of Hampson, found no significant differences for spirometric variables when compared ON and OFF states. Those results can be explained by the selection criteria applied to PD patients, their severity was mild to moderate and all patients that shown ATS/ERS diagnostic criteria for respiratory impairments were excluded.

Our meta-analysis fail to found significant conclusions when ON/OFF states were compared for FVC% and FEV_1%. Our results can be pooled due to the study of Hampson and their PD patient's profile that may not reflect the general characteristics of PD Patients.

Monteiro et al [25] carried out a meta-analysis, consisting of four trials with a total of 73 patients, and concluded that levodopa improved restrictive parameters of pulmonary dysfunction, probably due to an enhancement in chest wall compliance in the ON phase. These authors have also declared that obstructive parameters may improve with levodopa therapy; however, they stated that there is not enough evidence to support this view. Nakane et al [26] presented similar

results to ours, finding a significant improvement in PEF, maximal voluntary ventilation, FEV_1, FVC, and total lung capacity in PD patients receiving levodopa.

Limitations

The main limitation that emerged from this systematic review and meta-analysis is the lack of studies using the same variables to evaluate pulmonary impairments. Curiously, while spirometry is recognized as gold standard pulmonary function measure [27], only a couple of variables use to be reported by the different authors. Additionally the use of predicted versus non predicted scores makes difficult the comparisons among subjects impacting the results for meta-analysis. Another limitation for this review was the scare information about other respiratory variables like cough effectiveness or respiratory muscle strength. While therapeutic respiratory training programs are usually applied, there is a lack of knowledge about the real and concrete PD profile that is needed to be treated. In this line, is clear that a scientific and clinical consensus need to be published about the methods to assess respiratory function in PD patients including pulmonary, cough and respiratory muscle strength measures. Another limitation to this review is the lack of information provided about the concrete characteristics of PD, related to stage (early versus more advanced), time since diagnosis, and motor characteristics in the studies where PD patients and healthy subjects were compared. This can be the reason for the discordance between the studies included in the meta-analysis.

Conclusion

In summary, our results shown that PD patients have impaired respiratory capacities that are related to the PD severity, time since diagnosis and OFF state. When comparing groups (PD vs controls and ON vs OFF state) our meta-analysis fail to found significant conclusions, this can be explained by the heterogeneity of the inclusion criteria applied in each study and the scarce number of them. Our results suggest that spirometric studies as well as proper staging of PD may

be important factors to consider in future studies of respiratory function status in patients with PD. Nevertheless, further randomized controlled trials with attention to the stage of PD are necessary to evaluate the efficacy of levodopa on respiratory dysfunction in these patients.

Disclosure Statement

The authors do not have any conflict of interest.

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Author Contributions

MCV had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis, including and especially any adverse effects.
LLL contributed substantially to the study design, data analysis and interpretation, and the writing of the manuscript.
JRT had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
LPC contributed substantially to the study design, data analysis, interpretation, and the writing of the manuscript.
ICM contributed substantially to the study design, data analysis, interpretation, and the writing of the manuscript
RFR had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Figure leyends

Figure 1.-PRISMA 2009 Flow Diagram
Figure 2.- Differences between PD group and control group in FVC%
Figure 3.- Differences between PD group and control group in FEV1%
Figure 4.- Differences between PD ON group and PD OFF group in FVC%
Figure 5.- Differences between PD ON group and PD OFF group in FEV1%

Table 1. Newcastle Ottawa quality assessment scale for case/control studies

Study	Selection				Comparability (2)	Outcome			Total (9)
	Definition adequate (1)	Representativeness of the cases (1)	Selection ofcontrols (1)	Definition of controls (1)		Assessment (1)	Same methods of ascertainment (1)	Non-response rate (1)	
Baille G 2018	1	1	0	0	0	1	1	1	5
Tambasco N 2018	1	1	1	1	0	1	1	1	7
Hampson (2016)	1	1	1	0	0	1	1	1	6
Shaheen HA 2015	1	0	0	0	0	1	1	1	4
Sathyaprabha TN2005	1	1	1	1	0	1	1	1	7
Pandis MF 2002	1	1	1	1	0	1	1	1	7

Points for each quality measure given in parentheses with total reflecting the sun of these points.

Table 2. Characteristics of the observational studies on ventilatory impairment on Parkinson

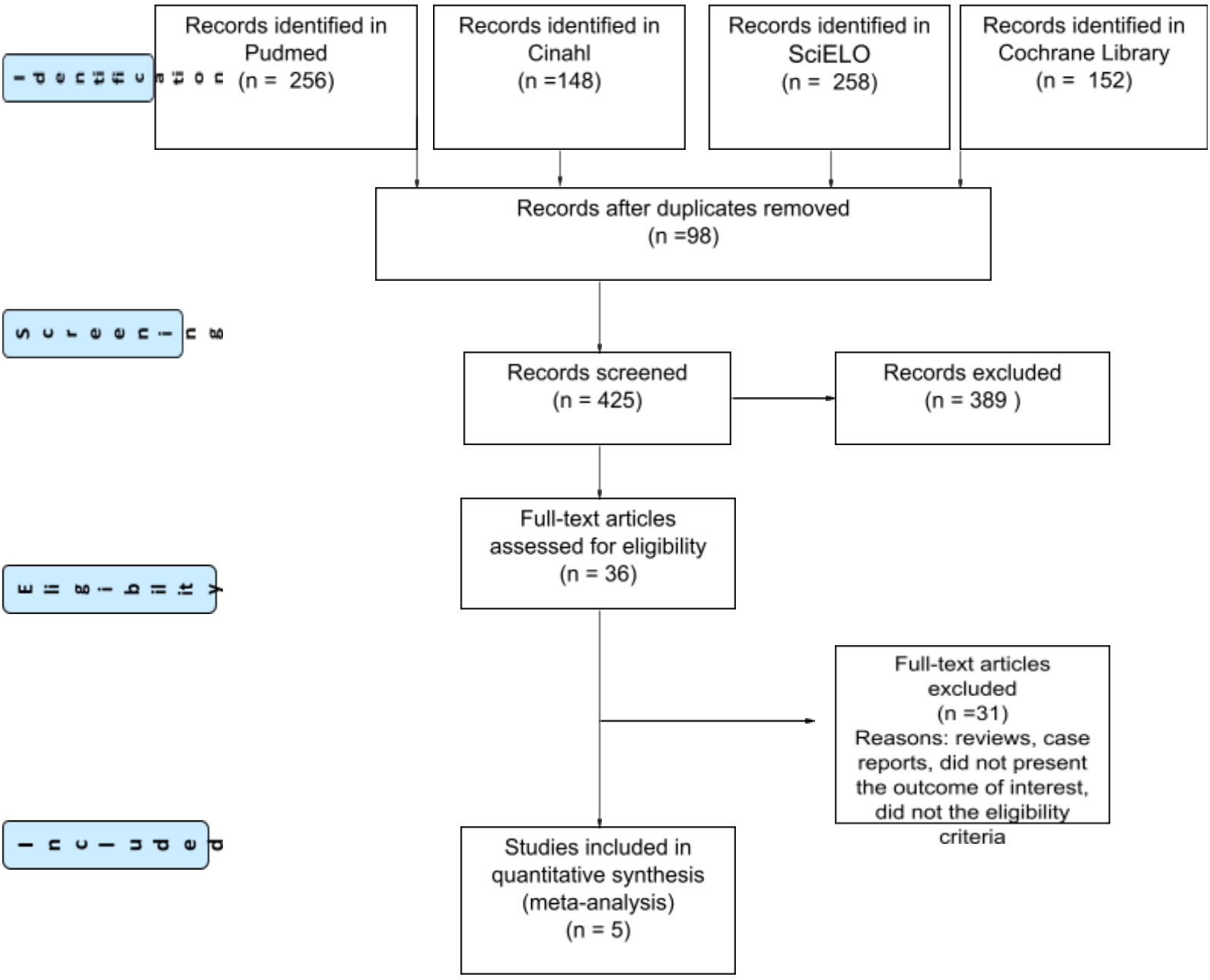
Author (year)	Design	Groups (n)	Mean age± SD	Disease duration (Years± SD)	Disease severity	Primary variables	Secondary variables	Results	
								Main results	Secondary results
Baille (2018)	Cross sectional case control study	-Tremor-dominant PD group (n=15) -Akinetic-dominant PD group (n=26) -Control group (n=36)	61.7 ± 7.7	1.9 ± 1.7	Mild to moderate	FVC%, FEV_1%	MIP %,SNIP%, FEV_1/FVC	FVC%: PD group > control group ($p<0.05$) FEV_1 %: PD group > control group NS	PD group< control group MIP% and SNIP% ($p<0.05$) FEV_1/FVC NS No differences between tremor and akinetic groups
Tambasco (2018)	Observational study	-PD ON (n=34) -PD OFF (n=34)	69.6 ± 7.3	10.4 ± 4.1	Moderate	FVC%, FEV_1%	FEV_1/FVC,VC%, RV%,TLC%,	PD ON group >PD OFF group ($p<0.05$)	PD ON group >PD OFF group ($p<0.05$)

Hampson (2017)	Cross sectional case control study	-PD ON group (n=86) -PD OFF group (n=86)	62.4±8.7	9.4	Mild to moderate	FVC%, FEV_1%	FEV_1/FVC%	PD ON group> PD OFFgroup (NS)	PD ON group> PD OFF group (p<0.05)
Shaheen (2009)	Cross sectional case control study	-PD group (n=30) -Control group (n=30)	67.7± 8.4	3±2.3	Moderate-severe	FVC%, FEV_1%	FEV_1/FVC	PD group< control group (p<0.05)	PD group< control group (p<0.05)
Sathyaprabha TN (2005)	Cross sectional case-control study	-PD ON group (n=35) -PD OFF group (n=35) -Control group (n=35)	51	No reported	Moderate	FVC%, FEV_1%	FEV_1/FVC, PEF%	Control group> PD group (p<0.05) PD ON group> PD OFF group (0.05)	Control group> PD group (p<0.05) PD ON group> PD OFF group (0.05)
De Pandis MF (2002)	Observational study	-PD ON (n=12) -PD OFF (n= 12)	67.66± 5.46	14.5± 0.66	Severe	FVC%,FEV_1%	FEV_1/FVC, PEF, FEF_{25-75}, FEF_{25},FEF_{50},FEF_{75} PaO_2, $PaCO_2$, and pH	PD ON group> PD OFF group (p<0.05)	PD ON group> PD OFF group pH,PaCO2 and PEF (p<0.05)

									Other variables NS

FVC%: Forced Vital Capacity predicted; FEV_1%: Forced expiratory volume in one second predicted; MIP: Maximal inspiratory mouth pressure; SNIP: Sniff nasal inspiratory pressure; VC: Vital capacity; RV: Residual volume; TLC: Total lung capacity; PEF: Peak expiratory flow rate; FEF: forced expiratory flow.

PRISMA 2009 Flow Diagram



From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). *P*referred *R*eporting *I*tems for *S*ystematic Reviews and *M*eta-*A*nalyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit www.prisma-statement.org.

Figure 2. Differences between PD group and control group in FVC%

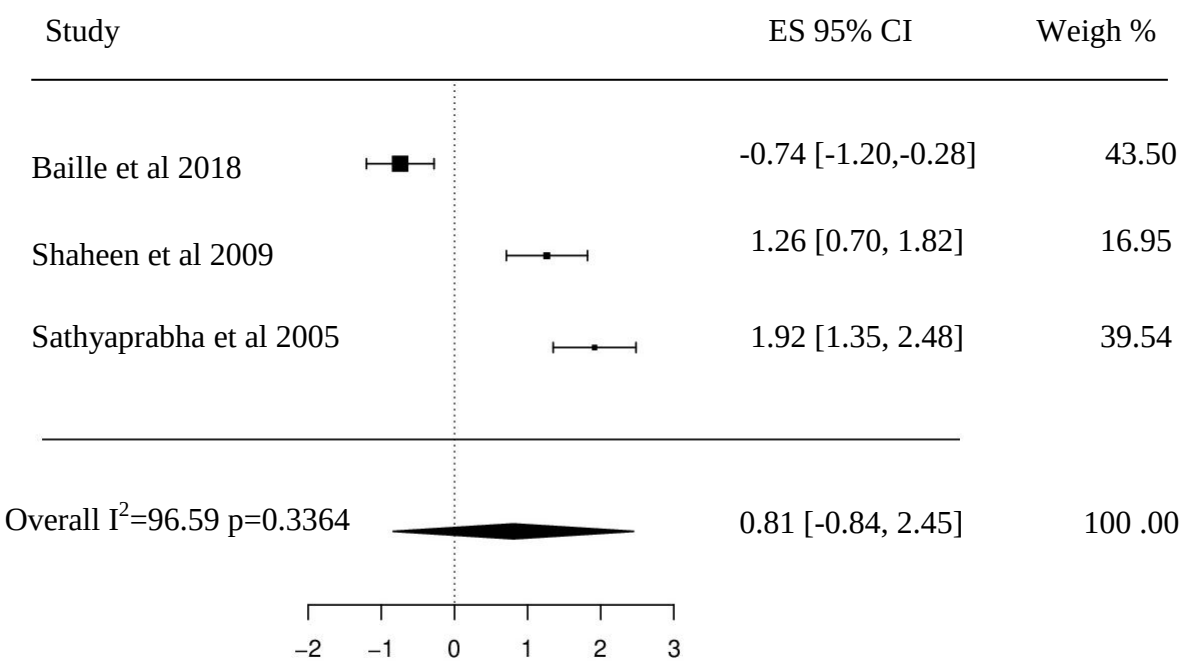


Figure 3. Differences between PD group and control group in FEV_1%

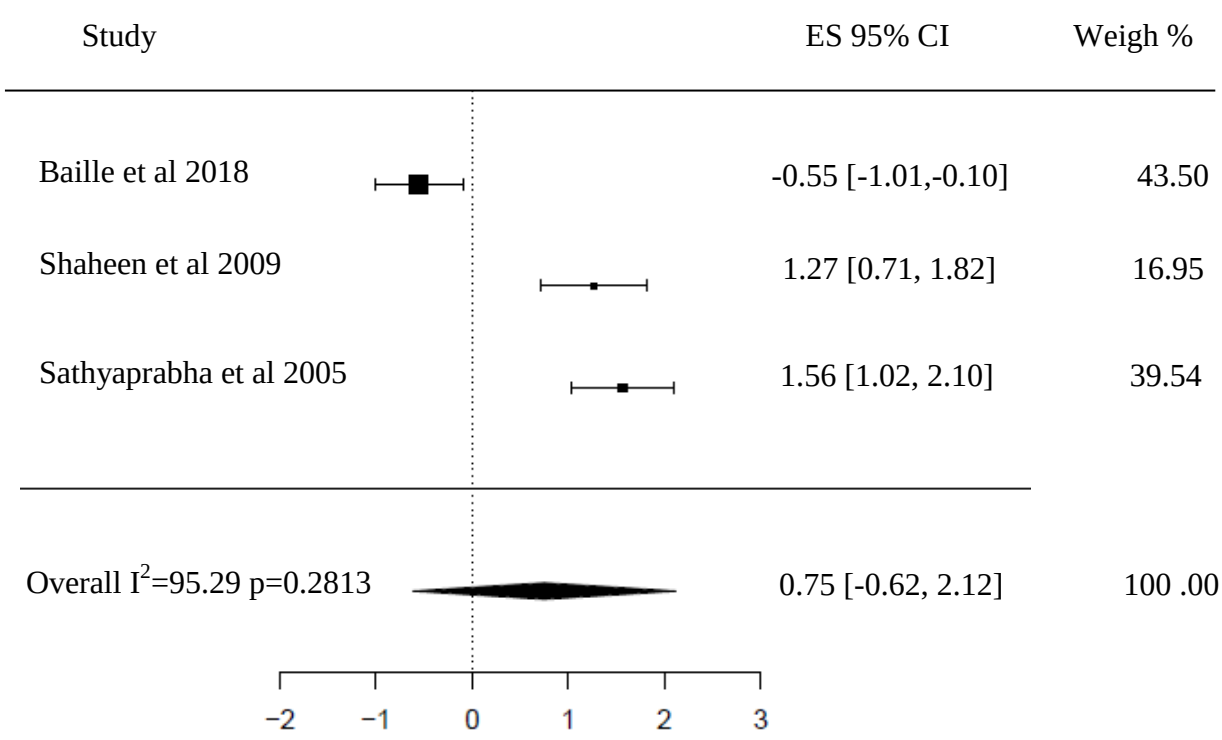


Figure 4. Differences between PD ON group and PD OFF group in FVC%

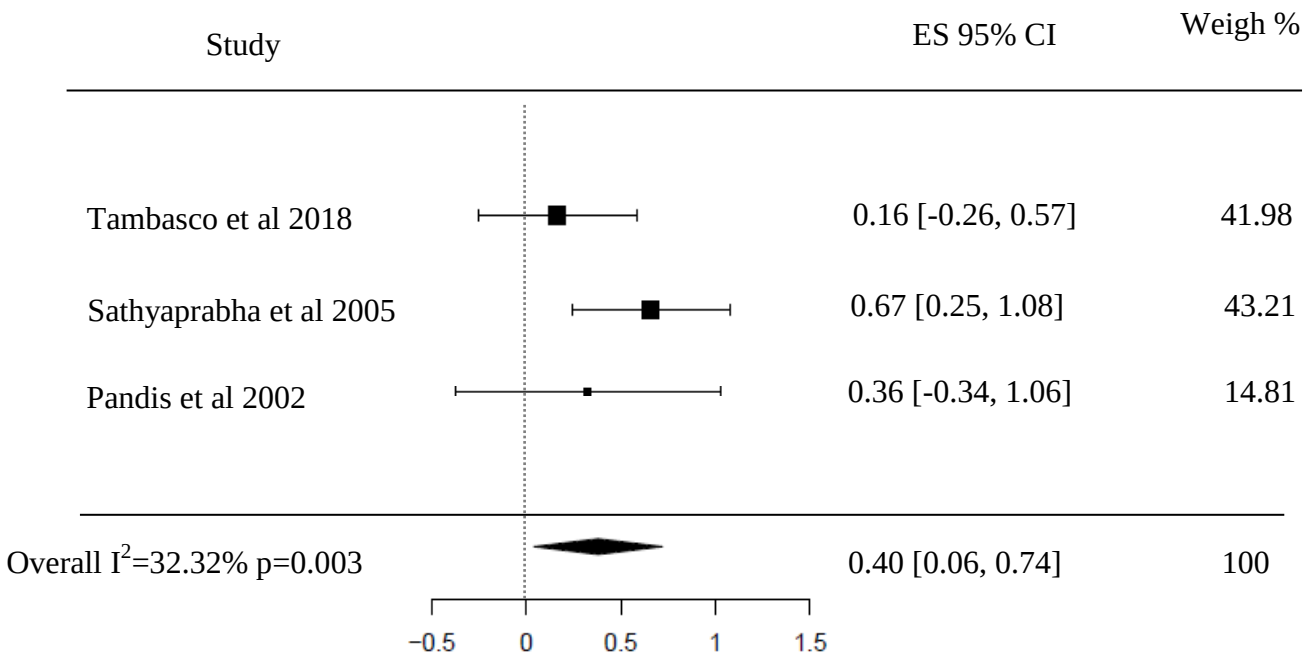


Figure 5. Differences between PD ON group and PD OFF group in FEV_1%